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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/530,843	04/08/2005	Susanne Leonhartsberger	LEONHARTSBERGER	3626

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EXAMINER	
SAIDHA, TEKCHAND	

ART UNIT	PAPER NUMBER
1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/530,843	LEONHARTSBERGER ET AL.	
	Examiner	Art Unit	
	Tekchand Saidha	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 May 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *May 17 2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

FINAL REJECTION

1. Amendment filed May 29, 2007 is acknowledged. Claims 1-8 are pending and under consideration in this examination.

2. The terminal disclaimer filed on May 29, 2007 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of any patent granted on reference pending application 10/530,844 filed on April 8, 2005 has been reviewed and is accepted. The terminal disclaimer has been recorded.

3. Applicant's arguments filed May 29, 2007 have been considered and not found to be persuasive. The reasons are discussed following the rejection(s).

4. Any objection or rejection of record which is not expressly repeated in this Office Action has been overcome by Applicant's response and withdrawn.

5. ***Sequence Rules***

It appears that Applicants have filed a CRF of the sequence listing along with a hard copy. See response filed May 29, 2007. However, the CRF is not yet made of record and is being investigated if the floppy disc (CRF) containing the sequence listing is received at the USPTO. Applicants will be notified shortly if the submitted computer readable form (CRF) of sequence listing has been received and is in compliance with the sequence rules.

6. Claim 8 objected to because of the following informalities: Claim 8, line 3, delete 'microbian' and replace with 'microbial'.

7. ***Claim Rejections - 35 USC § 112*** (second paragraph)

Claims 1-8 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point

out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is drawn to specific mutation corresponding to specific position of a sequence. However, there is no corresponding sequence or reference sequence present in the claim. The instant specification, page 4, indicated the reference sequence of the wild-type homoserine transsuccinylase to be SEQ ID NO: 2. Addition of SEQ ID NO: 2 as the corresponding reference sequence to claim 1 will overcome this rejection.

Claims 2-8 are included in the rejection for failing to correct the defect in the rejected base claim.

***** No response has been received*****

8. ***Written Description***

Claims 1-8 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Claims 1-8 (directly or indirectly) recite 'A mutant homoserine transsuccinylase or a MetA allele (or DNA) encoding the mutant homoserine transsuccinylase with specific amino acid residues modifications, plasmid and host cell comprising the MetA allele (or DNA). However, description to the reference homoserine transsuccinylase sequence of SEQ ID NO: 2 is lacking.

The specification, however, only provides the reference sequence of a single (single species) homoserine transsuccinylase sequence of SEQ ID NO: 2. The specification does teach a uniform numbering system of a specific SEQ ID NO:? other than SEQ ID NO: 2, that can be followed to mutate

positions 101 or 294 with respect to homoserine transsuccinylase from any source, in order to exhibit reduced sensitivity towards L-methionine or SAM, the genus claimed. Description of single species is insufficient to describe the claimed genus.

The specification therefore fails to describe additional representative species of these homoserine transsuccinylase by any identifying structural characteristics other than by name recited in claims, for which no predictability of structure is apparent. Given this lack of structure of the sequence(s) of the homoserine transsuccinylase or the encoding DNA or MetA allele, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention. Therefore, the written description requirement is not satisfied.

9. ***Enablement Rejection***

Claims 1-8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated mutant of homoserine transsuccinylase of SEQ ID NO: 2 (from *E. coli*) selected from a group consisting of Asp101Asn, Asp101His, Asp101Cys, Asp101Ser, Asp101Tyr, Asp101Ala, Asp101Ile; Tyr294Cys, Tyr294Leu, Tyr294Ala, Tyr294Pro, Tyr294Gln, Tyr294Lys or wherein Tyr294 is deleted, the encoding DNA, vector and isolated microbial host cell, wherein the mutants exhibit reduced sensitivity towards L-methionine or S-adenosyl methionine (SAM), does not reasonably provide enablement for any homoserine transsuccinylase wild-type enzyme, wherein the wild type enzyme possessing an amino acid sequence which comprises a constituent sequence AspGlyXaaXaaXaaThrGlyAlaPro between positions 90-115 and a

constituent sequence TyrGlnXaaThrPro between positions 285 and 310, wherein the mutation is an amino acid replacement of the Aspartate in the constituent sequence AspGlyXaaXaaXaaThrGlyAlaPro or an amino acid replacement in the constituent sequence TyrGlnXaaThrPro.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The scope of the claims does not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polynucleotides broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the nucleotide sequence and encoded amino acid sequence of SEQ ID NO: 2, and wherein the amino acid sequence is specifically modified at a position selected from the following mutations - Asp101Asn, Asp101His, Asp101Cys, Asp101Ser, Asp101Tyr, Asp101Ala, Asp101Ile; Tyr294Cys, Tyr294Leu, Tyr294Ala, Tyr294Pro, Tyr294Gln, Tyr294Lys or wherein Tyr294 is deleted.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions

or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications including the specific ones and with respect to any homoserine transsuccinylase wild-type enzyme from any source and have constituent amino acid sequence inserts AspGlyXaaXaaXaaThrGlyAlaPro or TyrGlnXaaThrPro at selected positions, because the specification does **not** establish: (A) regions of the any homoserine transsuccinylase structure which may be modified without effecting the mutants exhibiting reduced sensitivity towards L-methionine or S-adenosyl methionine (SAM); (B) the general tolerance of homoserine transsuccinylase to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any homoserine transsuccinylase enzyme residues with an expectation of obtaining the desired enzymatic or biological function capable of exhibiting reduced sensitivity towards L-methionine or S-adenosyl methionine (SAM); and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus there is high unpredictability associated with respect to modification(s) of the any of the homoserine transsuccinylase

sequences and from any source unless guidance is provided in establishing (A) - (D) as discussed above.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of exact nature of the mutant homoserine transsuccinylase, DNA (or polynucleotide) encoding a specific mutant homoserine transsuccinylase enzyme from any source and having the desired enzymatic characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Applicants argue the enzyme of claim 1 is defined by the mutation of Asp and Tyr at conserved sites of the protein plus a functional definition (i.e. the reduced sensitivity towards L-methionine or SAM). Some mutants of the wild-type enzyme and the methods to determine the feedback resistance are provided in the description wherein the conserved sites are replaced by various amine acids. Therefore, the scope of claim 1 is appropriate because a person skilled in the art can recognize that the mutants claimed in claim 1 achieve the purpose of the present application.

Applicants' arguments are considered but not found to be persuasive because the mutants are refer to specific positions the reference wild type sequence is not recognized by a person skilled in the art. This is because 'wild-type' is a general term and could be from '*E. coli*', 'human' or any other species,

and all species are not enabled or described with reference the mutations.

Based upon alignment of sequences provided in Appendix A of SAM sequences of 14 different species, Applicants argue that the alignment shows that in all these enzymes, Asp in position 101 and Tyr in Position 294 (both marked green) are conserved. In the light of this state of the art it is unnecessary to limit claim 1 to SEQ. ID. NO: 2, as claim 1 as written is in compliance with 35 USC §112.

Green Markings are displayed black on the 'Image File Wrapper' - that is available for the examiner to view and therefore not legible. Assuming even if the Applicants are correct that Asp in position 101 and Tyr in Position 294 are conserved in fourteen different species, still there is no evidence of the homoserine transsuccinylase sequences from any source having the same residue at the position indicated. There is clearly no numbering system that is established in order for one of skill in the art to determine that a specific amino acid position of the homoserine transsuccinylase in one species is equivalent to another in a different species. The rejections are therefore maintained.

10. No claim is allowed.

11. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the

date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tekchand Saidha whose telephone number is (571) 272 0940. The examiner can normally be reached on 8.30 am - 5.00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on (571) 272 0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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